REMARKS

The Office Action mailed November 5, 2002, has been received and reviewed. Claim 27 having been amended, the pending claims are claims 27-39. The amendment to claim 27 is made to clarify the claimed invention.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 36, 37, and 39 under 35 U.S.C. §102(b) as being anticipated by Ruenitz et al. (J. Med. Chem. 39:4853-4859 (1996)). This rejection is respectfully traversed.

The Examiner asserts that Ruenitz et al. teaches a compound of the structural formula recited in the claims (compound **9** in scheme 1, known as "HPPA") but acknowledges that the reference does not explicitly describe a pharmaceutical composition comprising this compound. Because the compound is tested in two *in vitro* systems that act to model a physiological system, the Examiner concludes that the tests inherently comprise compound **9** and a pharmaceutically acceptable carrier.

Applicant respectfully disagrees that Ruenitz et al. inherently disclose compound **9** in a pharmaceutically acceptable carrier. Ruenitz et al teach compound **9** in only three forms. First, compound **9** is taught as a beige crystal (Ruenitz et al., page 4858, first column, first full paragraph). Second, Ruenitz et al. teach compound **9** in a growth medium for cell-free competitive assays. This composition included cytosol from immature rat uterus and tritiated estradiol (Ruenitz et al., page 4858, second column, first full paragraph). Third, Ruenitz et al. teach incubation wells contained MCF-7 cells, serum-free medium containing tritiated estradiol, and the test compounds (e.g., compound **9**) (Ruenitz et al., page 4858, second column, second full paragraph). These systems are designed to mimic physiological systems, but because the compositions contain components such as rat cytosol and tritiated estradiol, it is respectfully submitted that none of the compositions taught in Ruenitz et al. comprise compound **9** and a carrier that is pharmaceutically acceptable.

Reconsideration and withdrawal of the rejection of claims 36, 37, and 39 under 35 U.S.C. §102(b) as being anticipated by Ruenitz et al. (J. Med. Chem. 39:4853-4859 (1996) is accordingly requested.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 27, 28, and 30-35 under 35 U.S.C. §103(a) as being unpatentable over Ruenitz et al. (J. Med. Chem. 39:4853-4859 (1996)), as applied to claims 36, 37 and 39 above, and further in view of Ruenitz (US Pat. No. 5,189,212). This rejection is respectfully traversed.

The Examiner notes that Ruenitz et al. teaches that compound **9** (referenced above) is a full estrogen with potency approaching compound **8** (known as 4HTA), an unsaturated triarylethylene compound similar in structure. The Examiner further states that Ruenitz '212 teaches a genus of estrogenic triarylethylene compounds (including 4HTA) that have utility in treating disorders responsive to estrogen, such as osteoporosis. The Examiner concludes that it would have been obvious to a skilled artisan to administer estrogenic compound **9** to a peri/post menopausal female to treat disorders responsive to estrogen, such as osteoporosis.

Applicant respectfully disagrees; however claim 27 has been amended to clarify that the compound used in the treatment is *nonuterotrophic*. Applicants submit that it would not have been obvious to one of skill in the art, in view of the cited references, that compound **9** is nonuterotrophic. Hence it would not have been obvious to use compound **9** to treat disorders involving *extra-reproductive tract tissues* (claim 27) wherein a lack of uterotrophic effects would be desirable.

Applicants acknowledge that Ruenitz '212 teaches that 4HTA has estrogenic activity and can be used to treat conditions associated with a low level of estrogen. However, 4HTA (compound **8**) was later characterized in Ruenitz et al. as a partial agonist having some antagonistic potency (Ruenitz et al., abstract, page 4853). Compound **9**, on the other hand, was shown to be a full agonist in stimulating growth (102% maximal growth-stimulatory effect, as a percent of that of estradiol) (Ruenitz et al., abstract, page 4853, and Table 2) and did not function as an estrogen antagonist in the growth inhibition assay (Ruenitz et al., page 4855, first column). Ruenitz et al. teach a lack of uterotrophic effects attributable to compound **8** (4HTA) (page 4855, last full paragraph--note however that 4HTA was subsequently found to be moderately uterotrophic as described in the present specification), but there is no teaching or suggestion in Ruenitz et al. that compound **9** (HPPA) is likewise nonuterotrophic.

Structural differences between compound 8 and compound 9 (e.g., unsaturated vs. saturated bonds) make it dangerous to conclude that the pharmakodynamics and/or pharmacokinetics exhibited by one compound (e.g., compound 8) are necessarily predictive of those characteristics in the other (compound 9). In fact, the finding in the present invention that HPPA is not uterotrophic was quite unexpected in view of the reproductive tract effects that routinely accompany the administration of other known estrogens and estrogenic compounds. The specification at page 10, lines 7-27, states:

> *Characterization and comparison of HPPA and 4HTA.* HPPA and its unsaturated analog 4HTA differ in their relative estrogen receptor binding affinities (RBA), exhibiting RBAs of 0.20 and 20 percent of estradiol binding affinity, respectively (P. Ruenitz et al., J. Med. Chem. 39: 4853-4859 (1996)). Nonetheless, both HPPA and 4HTA are potent stimulators of cell proliferation in MCF 7 human breast cancer cells, and HPPA, although it exhibits a relatively low estrogen receptor affinity, is considered a "full estrogen" by virtue of its ability to eventually stimulate maximal growth of MCF 7 cells to a level equal to that attained by estradiol (P. Ruenitz et al., J. Med. Chem. 39: 4853-4859 (1996)). Additionally, 4HTA is a mild antiestrogen in that it weakly inhibits estradiol-stimulated proliferation of MCF 7 human breast cancer cells; in contrast, HPPA shows no activity as an antiestrogen.
>
> The two compounds also differ in their effect on bone tissue *in vivo*. Despite its high estrogen receptor affinity and estrogenic potency in stimulating MCF-7 cell proliferation, 4HTA shows no bone protective effect in the OVX rat, contrary to the erroneous report in P. Ruenitz et al. (J. Med. Chem. 39: 4853-4859 (1996)); it is ineffective in preventing loss of cancellous bone volume or elevation of serum osteocalcin after ovariectomy (see Example III). HPPA, on the other hand, shows significant bone protective estrogenicity. Moreover, and very advantageously, HPPA has been discovered to be nonuterotrophic. This stands in contrast to 4HTA, which is, in fact, moderately uterotrophic, notwithstanding statements to the contrary in P. Ruenitz et al., J. Med. Chem. 39: 4853-4859 (1996). The finding that HPPA is not uterotrophic was quite unexpected in view of the reproductive tract effects that routinely accompany the administration of other known estrogens and estrogenic compounds (Table 1).

Further, at page 30, lines 6-16, the specification states:

> HPPA exhibits a bioactivity profile that was neither evident nor predictable from its chemical structure: relatively low ER affinity, full estrogenicity in the MCF-7 cell proliferation assay, not inhibitory of estrogen-stimulated cell proliferation, and significant estrogenic skeletal and cardiovascular effects *in vivo*; yet despite all these systemic effects characteristic of an estrogen mimetic, HPPA is

substantially non-uterotrophic. This bioactivity profile is unique among candidate drugs for ERT. Other compounds which stimulate growth of estrogen responsive cells *in vitro* (e.g., in the MCF 7 cell proliferation assay) exhibit reproductive tract estrogenicity (Table 1; P. Ruenitz, Female sex hormones and analogs. In: Wolff, M. E., Ed. Burger's Medicinal Chemistry and Drug Discovery, Fifth Edition, vol 4. New York: John Wiley & Sons: 1997; 553-587), but HPPA, a full estrogen agonist in MCF-7 cells, did not appear to be uterotrophic in the animal model.

It is accordingly submitted that claims 27, 28 and 30-35 are not obvious over Ruenitz et al. (J. Med. Chem. 39:4853-4859 (1996)), as applied to claims 36, 37 and 39 above, and further in view of Ruenitz (US Pat. No. 5,189,212). Reconsideration and withdrawal of claims 27, 28 and 30-35 under 35 U.S.C. §103(a) is respectfully requested.

Allowable Claims

Applicant acknowledges with appreciation that claims 29 and 38 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim. Applicant believes the base claims (claims 27 and 36, respectively) are now in condition for allowance, and respectfully submit that, as a result, claims 29 and 38 are also in now condition for allowance without amendment.

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Summary

It is respectfully submitted that the pending claims are 27-39 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on this 7 day of April, 2003, at 1:30pm (Central Time).

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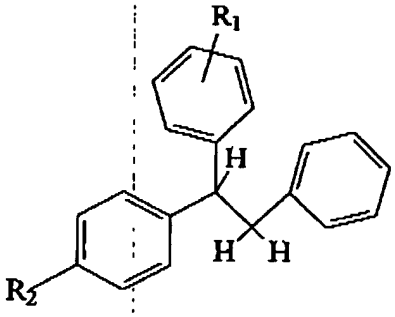
APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/981,617
Docket No.: 235.00060102

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

In the Claims

For convenience, all pending claims are shown below.

27. (Amended) A method for treating extra-reproductive tract tissues that are responsive to treatment with estrogen comprising administering to a patient an effective amount of a nonsteroidal compound having the structure



(I)

wherein R_1 is $-O(CH_2)_mR_3$ or $-(CH_2)_nR_3$; R_3 is an anionic substituent; m is 1, 2, 3 or 4; n is 0, 1, 2, 3 or 4; and R_2 is [H or] para-OH[; and wherein each of R_1 and R_2 is independently meta or para to its respective phenyl-ethyl linkage].

28. The method of claim 27 wherein R_1 is $-O(CH_2)_mR_3$.

29. The method of claim 27 wherein R_1 is $-(CH_2)_nR_3$.

30. The method of claim 27 wherein the compound is 4-[1-(4-hydroxyphenyl)-2-phenylethyl]phenoxyacetic acid such that R_1 is para-OCH_2R_3; and R_3 is $-COO^-$.

31. The method of claim 27 wherein the anionic substituent comprises a functional group selected from the group consisting of a carboxylate group, a tetrazolate group and a bisphosphonate group.

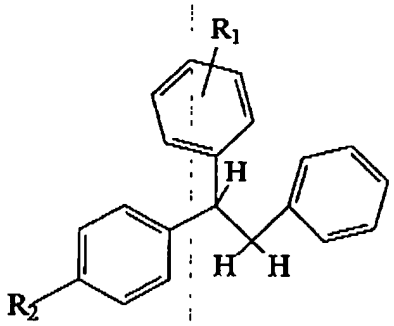
32. The method of claim 27 wherein the patient is a female.

33. The method of claim 32 wherein the patient is a perimenopausal or postmenopausal female.

34. The method of claim 27 wherein the compound is administered in an estrogen replacement therapy.

35. The method of claim 27 wherein the compound is administered to treat osteopenia.

36. A pharmaceutical composition comprising a compound having the structure



(I)

wherein R_1 is $-O(CH_2)_mR_3$ or $-(CH_2)_nR_3$; R_3 is an anionic substituent; m is 1, 2, 3 or 4; n is 0, 1, 2, 3 or 4; and R_2 is para-OH; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

37. The pharmaceutical composition of claim 36 wherein R_1 is $-O(CH_2)_mR_3$.

38. The pharmaceutical composition of claim 36 wherein R_1 is $-(CH_2)_nR_3$.

39. The pharmaceutical composition of claim 36 wherein the compound is 4-[1-(4-hydroxyphenyl)-2-phenylethyl]phenoxyacetic acid such that R_1 is para-OCH_2R_3; and R_3 is $-COO^-$.